CLAIMS

What is claimed is:

1. A method for eliminating at least a substantial portion of a clonal T cell subpopulation from a mixed population of T cells from an individual, comprising,

exposing a population of cells, wherein at least a portion thereof comprises T cells, to one or more pro-apoptotic or growth inhibiting compositions wherein said exposure induces apoptosis or growth inhibition in at least a substantial portion of at least one clonal T cell population present in the mixed population of T cells;

thereby eliminating at least a substantial portion of said clonal T cell population from the mixed population of T cells.

2. The method of claim 1 further comprising expanding the remaining mixed population of T cells.

3. The method of claim 2 wherein the remaining mixed population of cells is expanded by exposing the remaining mixed population of cells to a surface wherein the surface has attached thereto one or more agents that ligate a cell surface moiety of at least a portion of the remaining T cells and stimulates said remaining T cells.

4. The method of claim 3, wherein said surface has attached thereto a first agent that ligates a first T cell surface moiety of a T cell, and the same or a second surface has attached thereto a second agent that ligates a second moiety of said T cell, wherein said ligation by the first and second agent induces proliferation of said T cell.

5. A population of T cells generated according to the method of any one of claims 1 - 3.

6. The method of claim 1 wherein the pro-apoptotic or growth inhibiting composition comprises an autoantigen.

7. The method of claim 6, wherein the autoantigen is selected from the group consisting of myelin basic protein (MBP), MBP 84-102, MBP 143-168, pancreatic islet cell antigens, collagen, thyroid antigens, Scl-70, nucleic acid, acetylcholine receptor, S Antigen, and type II collagen.

8. The method of claim 1 wherein the pro-apoptotic composition comprises allogeneic or xenogeneic cells.

9. The method of claim 1 wherein said population of cells, wherein at least a portion thereof comprises T cells, is exposed to one or more pro-apoptotic compositions *in vivo*.

10. The method of claim 1 wherein said population of cells, wherein at least a portion thereof comprises T cells, is exposed to one or more pro-apoptotic compositions *ex vivo*.

11. The method of claim 3 wherein the exposure of said cells to said surface is for a time sufficient to increase polyclonality.

12. The method of claim 11 wherein the increase comprises a shift from mono to oligoclonality or to polyclonality of the T cell population as measured by a Vβ, Vα, Vγ, or Vδ spectratype profile of at least one Vβ, Vα, Vγ, or Vδ family gene.

13. A population of T cells generated according to the method of claim 6 or 11.

14. A method for treating autoimmune disease in a patient comprising administering to the patient the population of T cells of claim 13.

15. The method of claim 14 wherein the patient has been treated with an immunoablative agent prior to administering the population of T cells of claim 10.

16. The method of claim 15 wherein the immunoablative agent is selected from the group consisting of campath, anti-CD3 antibodies, cyclophosphamide, fludarabine, cyclosporine, FK506, mycophenolic acid, steroids, FR901228, and irradiation.

17. The method of claim 14 wherein the patient has been treated with a T cell ablative therapy prior to administering the population of T cells of claim 10.

18. The method of claim 1 wherein the pro-apoptotic or growth inhibiting composition comprises one or more compositions selected from the group consisting of, anti-CD3 antibody, anti-CD2 antibody, anti-CD20 antibody, target antigen, MHC-peptide tetramers or dimers, Fas ligand, anti-Fas antibody, IL-2, IL-4, TRAIL, rolipram, doxorubicin, chlorambucil, fludarabine, cyclophosphamide, azathioprine, methotrexate, cyclosporine, mycophenolate, FK506, inhibitors of bcl-2, topoisomerase inhibitors, interleukin-1β converting enzyme (ICE)-binding agents, Shigella IpaB protein, staurosporine, ultraviolet irradiation, gamma irradiation, tumor necrosis factor, target antigens nucleic acid molecules, proteins or peptides, and non-protein or non-polynucleotide compounds.

19. The method of claim 3, wherein at least one agent is an antibody or an antibody fragment.

20. The method of claim 3, wherein the first agent is an antibody or a fragment thereof, and the second agent is an antibody or a fragment thereof.

21. The method of claim 3, wherein the first and the second agents are different antibodies.

22. The method of claim 3, wherein the first agent is an anti-CD3 antibody, an anti-CD2 antibody, or an antibody fragment of an anti-CD3 or anti-CD2 antibody.

23. The method of claim 3, wherein the second agent is an anti-CD28 antibody or antibody fragment thereof.

24. The method of claim 3, wherein the first agent is an anti-CD3 antibody and the second agent is an anti-CD28 antibody.

25. A method for eliminating at least a substantial portion of a clonal T cell subpopulation from a mixed population of T cells from an individual, comprising,

(a) exposing a population of cells wherein at least a portion thereof comprises T cells to one or more compositions that sensitize at least a portion of the T cells to further activation or stimulation,

(b) exposing the population of cells to a surface wherein the surface has attached thereto one or more agents that ligate a cell surface moiety of at least a portion of the sensitized T cells and stimulates said sensitized T cells, wherein the exposure of said sensitized T cells to said surface is for a time sufficient to induce apoptosis of said sensitized T cells;

thereby eliminating said sensitized T cells from the population.

26. The method of claim 25 wherein step (b) further comprises exposing said population of cells to said surface for a time sufficient to stimulate at least a portion of the remaining T cells and wherein said at least a portion of the remaining cells proliferates.

27. The method of claim 25, wherein said surface has attached thereto a first agent that ligates a first T cell surface moiety of a T cell; and the same or a second surface has attached thereto a second agent that ligates a second moiety of said T cell, wherein said ligation by the first and second agent induces proliferation of said T cell.

28. The method of claim 26 wherein the exposure of said cells to said surface is for a time sufficient to increase polyclonality.

29. The method of claim 28 wherein the increase comprises a shift from mono to oligoclonality or to polyclonality of the T cell population as measured by a Vβ, Vα, Vγ, or Vδ spectratype profile of at least one Vβ, Vα, Vγ, or Vδ family gene.

30. A population of T cells generated according to the method of claim 25 or 28.

31. The method of claim 25 wherein the individual requires a hematopoietic stem cell transplant.

32. The method of claim 31, wherein the composition that sensitizes comprises recipient PBMCs that have been treated such that they are unable to continue dividing and the population of cells comprises donor T cells.

33. A population of T cells generated according to the method of claim 32.

34. A method for reducing the risk of, or the severity of, an adverse GVHD effect in a patient who is undergoing a hematopoietic stem cell transplant, comprising administering to said patient the population of T cells according to claim 30 or 33.

35. The method of claim 25 wherein the individual requires an organ transplant.

36. The method of claim 35 wherein the composition that sensitizes comprises donor cells that have been treated such that they are unable to divide and the population of cells comprises recipient T cells.

37. The method of claim 36 wherein the exposure of said cells to said surface is for a time sufficient to increase polyclonality.

38. The method of claim 37 wherein the increase comprises a shift from mono to oligoclonality or to polyclonality of the T cell population as measured by a Vβ, Vα, Vγ, or Vδ spectratype profile of at least one Vβ, Vα, Vγ, or Vδ family gene.

39. A population of T cells generated according to the method of claim 36 or 37.

40. A method for reducing the risk of organ rejection in a patient who is receiving an organ transplant, comprising administering to the patient the population of T cells of claim 39.

41. The method of claim 40 wherein the patient has been treated with a T cell ablative therapy prior to administration of the population of T cells of claim 36.

42. The method of claim 25 wherein the composition that sensitizes comprises an autoantigen.

43. The method of claim 42, wherein the autoantigen is selected from the group consisting of myelin basic protein (MBP), MBP 84-102, MBP 143-168, Scl-70, pancreatic islet cell antigens, S Antigen; and type II collagen.

44. The method of claim 43 wherein the exposure of said cells to said surface is for a time sufficient to increase polyclonality.

45. The method of claim 44 wherein the increase comprises a shift from mono to oligoclonality or to polyclonality of the T cell population as measured by a Vβ, Vα, Vγ, or Vδ spectratype profile of at least one Vβ, Vα, Vγ, or Vδ family gene.

46. A population of T cells generated according to the method of claim 42 or 44.

47. A method for treating autoimmune disease in a patient comprising administering to the patient the population of T cells of claim 46.

48. The method of claim 47 wherein the patient has been treated with a T cell ablative therapy prior to administering the population of T cells of claim 46.

49. The method of claim 26, wherein at least one agent is an antibody or an antibody fragment.

50. The method of claim 26, wherein the first agent is an antibody or a fragment thereof, and the second agent is an antibody or a fragment thereof.

51. The method of claim 50, wherein the first and the second agents are different antibodies.

52. The method of claim 26, wherein the first agent is an anti-CD3 antibody, an anti-CD2 antibody, or an antibody fragment of an anti-CD3 or anti-CD2 antibody.

53. The method of claim 26, wherein the second agent is an anti-CD28 antibody or antibody fragment thereof.

54. The method of claim 26, wherein the first agent is an anti-CD3 antibody and the second agent is an anti-CD28 antibody.

55. A method for generating a substantially pure population of $CD3^+/CD28^+$ T cells from a population of T cells from an individual, comprising:

exposing a population of cells, wherein at least a portion thereof comprises T cells, *ex vivo* to a composition that stimulates and/or selects surface CD3 and CD28 molecules;

thereby generating a substantially pure population of $CD3^+/CD28^+$ T cells.

56. A method for generating a substantially pure population of $CD4^+/CD3^+/CD28^+$ T cells from a population of T cells from an individual, comprising:

exposing a population of cells, wherein at least a portion thereof comprises T cells, *ex vivo* to a composition that stimulates and/or selects surface CD3 and CD28 molecules;

thereby generating a substantially pure population of $CD4^+/CD3^+/CD28^+$ T cells.

57. A method for generating a substantially pure population of $CD8^+/CD3^+/CD28^+$ T cells from a population of T cells from an individual, comprising:

exposing a population of cells, wherein at least a portion thereof comprises T cells, *ex vivo* to a composition that stimulates and/or selects surface CD3 and CD28 molecules;

thereby generating a substantially pure population of $CD8^+/CD3^+/CD28^+$ T cells.

58. The method of any one of claims 55-57 further comprising expanding said CD3+CD28+ T cells for a time sufficient such that the percentage of contaminating $CD3^+/CD28^-$ T cells is less than about 5%.

59. The method of any one of claims 55-57 further comprising expanding said CD3+CD28+ T cells for a time sufficient such that the percentage of contaminating $CD3^+/CD28^-$ T cells is less than about 1%.

60. The method of any one of claims 55-57 further comprising expanding said CD3+CD28+ T cells for a time sufficient such that the percentage of contaminating $CD3^+/CD28^-$ T cells is less than 0.1%.

61. The method of any one of claims 55-57 wherein the CD3 molecule is stimulated using an anti-CD3 antibody and the CD28 molecule is stimulated using an anti-CD28 antibody.

62. A method for activating and expanding a population of T cells by cell surface moiety ligation, comprising:

contacting a population of cells, wherein at least a portion thereof comprises T cells, with a surface, wherein said surface has attached thereto one or more agents that ligate a cell surface moiety of at least a portion of the T cells and stimulates said T cells, wherein said surface is present at a ratio of said surface to said cells such that at least a substantial portion of at least one population of antigen-specific T cells is deleted after about 8 days of culture.

63. The method of claim 62 wherein said ratio is from about 10:1 to about 5:1.

64. The method of claim 62 wherein said ratio is about 5:1.

65. The method of claim 62 wherein said ratio is about 10:1.

66. The method of claim 1 further comprising expanding the mixed population of T cells, comprising,

exposing the remaining mixed population of T cells to the pro-apoptotic composition, wherein said exposure induces proliferation in the mixed population of T cells.

67. The method of claim 66 wherein said pro-apoptotic composition comprises anti-CD3 and anti-CD28 antibodies co-immobilized on a bead.